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(54) MULTI-SITE METAL CHELATING AGENTS

MEHRZÄHNIGE METALL-CHELATIERENDE VERBINDUNGEN

AGENTS CHELATEURS METALLIQUES MULTI-SITES

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Description

This invention relates to polychelants, that is multi-site metal chelating agents, and chelates formed therewith, as well as to their preparation, compositions containing them and their use, especially in medicine, in particular in diagnostic imaging. The invention relates especially to the use of metal chelates of such polychelants as contrast agents in X-ray imaging and Magnetic Resonance Imaging (MRI).

BACKGROUND OF THE INVENTION

Contrast agents may be administered in medical imaging procedures, for example X-ray, magnetic resonance and ultrasound imaging, to enhance the image contrast in images of a subject, generally a human or non-human animal body. The resulting enhanced contrast enables different organs, tissue types or body compartments to be more clearly observed or identified. In X-ray imaging the contrast agents function by modifying the X-ray absorption characteristics of the body sites in which they distribute; magnetic resonance contrast agents generally function by modifying the characteristic relaxation times T_1 and T_2 of the nuclei, generally water protons, from the resonance signals of which the images are generated; and ultrasound contrast agents function by modifying the speed of sound or the density in the body sites into which they distribute.

The X-ray contrast agents first developed, barium sulfate and sodium iodide, have been superseded by iodinated organic compounds, in particular triiodophenyl compounds. Improvements in systemic toxicity over the last 40 years have also been achieved by the development of non-ionic iodinated X-ray contrast agents (see Shaw in "Radiopaques", CRC Handbook of Vitamins, Hormone and Radiopaques, CRC Press, p. 229-243). More recent improvements have come from the development of the so-called dimer X-ray contrast agents, compounds containing two triiodophenyl moieties per molecule (see McClennan in Introduction to Supplement in Investigative Radiology, 19; S289-S292 (1984)).

As the X-ray absorption cross-sections of the elements generally increase with increasing atomic number and as such cross-sections are dependent on the wavelength of the X-rays there has been some desire to utilize the X-ray absorption properties of the lanthanides and other high atomic number metals to develop contrast agents with improved X-ray attenuation especially at the wavelengths used in CT; however these attempts have generally been relatively unsuccessful.

Thus, for example, Nalbandian et al. (see Ann. N.Y. Acad. Sci. 78: 779 (1959)) and Shapiro et al. (see Ann. N.Y. Acad. Sci. 78: 756 (1959)) proposed the use of the diethylenetriaminepentaacetic acid (DTPA) chelate of bismuth (BiDTPA) and the ethylenediaminetetraacetic acid (EDTA) chelate of lead (PbEDTA) as radiographic contrast agents but encountered problems of solubility and toxicity. In US-A-4176173 Winchell et al. described the use of simple hafnium or tantalum complexes as X-ray contrast agents and more recently, ytterbium DTPA has been studied as an intravascular X-ray contrast agent, and an LD_{50} of 10 mmoles/kg has been reported (see Unger et al. Invest. Radiol. 21: 802 (1986)).

In MRI, the use of paramagnetic metal ions, such as Mn(II), as contrast agents was first proposed by Lauterbur et al. in 1978 (see pages 752-759 in "Electrons to Tissues - Frontiers of Biological Energetics" Vol. 1, edited by button et al., Academic Press, NY, 1978) and more recently Schering AG in US-A-4647447 proposed the use of salts of gadolinium(III) chelates of DTPA.

EP-A-0255471 describes the use of various metal complexes of macrocyclic compounds as contrast agents.

In order to achieve tissue-specific MRI contrast enhancement or to enhance relaxivity the coupling of paramagnetic chelates, such as GdDTPA, or metal complexing groups to macromolecular carriers or biomolecules, such as polysaccharides, proteins, antibodies, liposomes, enzymes, polyethyleneimines etc. has been proposed by several researchers - see for example EP-A-130934 (Schering), EP-A-136812 (Technicare), EP-A-184899 (Nycomed), EP-A-186947 (Nycomed), EP-A-277088 (Schering), EP-A-305320 (Schering), WO-A-88/07521 (Schering), WO-A-88/08422 (Schering), WO-A-85/05554 (Amersham), WO-A-89/06979 (Nycomed), EP-A-331616 (Schering) and Schmiedl et al. Radiology 162:205 (1987) . Furthermore, WO-A-88/01178 (Dow) discloses attempts made to chelate metal ions with carboxylate-terminal "starburst dendrimers" and to conjugate antibodies to such dendrimers, however the therapeutic or diagnostic utility of such structures has not been established.

The visualization of certain disease states such as cancer can benefit particularly from the use of tissue targeting contrast agents. Thus for example, in MRI it may be necessary to deliver 100-1000 paramagnetic centres to a tumour to obtain sufficient relaxation enhancement for visualization. Macromolecular polychelates for use in this regard have been proposed but attempts to prepare such macromolecular polychelates and then to attach them to target-specific proteins such as antibodies have not met with great success (see for example Manabe et al. in Biochimica et Biophysica Acta 883: 460 (1986) and Schreve et al. in Magnetic Resonance in Medicine 3: 336 (1986)).

Thus, a need still remains for alternative contrast agents with reduced toxicity, enhanced contrast characteristics and/or modified biological properties and, more especially in the field of X-ray contrast agents, significant opportunity exists for improvement in the reduction of contrast media cost and toxicity, in the reduction of patient discomfort and in

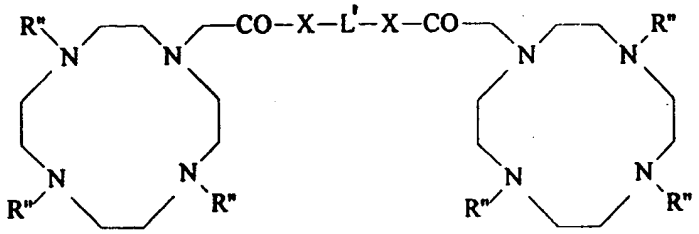
the reduction of the incidence of side reactions, enzymatic deiodination, etc.

The disclosures of each of the publications and other documents referred to above, as well as each of those referred to hereinafter, are incorporated by reference in the present specification.

SUMMARY OF THE INVENTION

We have now found that metal, e.g. heavy metal or paramagnetic metal, chelates of a range of novel oligomeric polychelants comprising two macrocyclic chelants linked together via a linker moiety are particularly suited to use as imaging contrast agents, and especially, in the case of heavy metal chelates, as X-ray contrast agents.

Thus viewed from one aspect the invention provides an oligomeric polychelant of formula I



(I)

(wherein XL'X is a linker moiety in which each X is oxygen or a secondary, tertiary or ring nitrogen and the molecular weight of XL'X is less than 1000; R" is a group $-CH_2COR$ in which R is OR' or NR'_2 where each R' independently is hydrogen or an alkyl, cycloalkyl, alkenyl, alkynyl or aryl group optionally substituted by hydroxyl, amine or carboxyl groups, or a carbohydrate group, a peptide or polypeptide residue, a protein or a biomolecule) or a salt or chelate thereof.

The invention thus particularly provides metal chelates which are the chelate complexes of polychelants according to the invention and metal ions, preferably two metal ions.

The novel oligomeric polychelants and the metal chelates and polychelates formed therefrom are useful in a variety of biomedical contexts including magnetic resonance imaging, X-ray/CT imaging, nuclear medicine and heavy metal detoxification in mammals. The polychelants comprise a multiplicity of chelating sites whereby more than one metal ion may be complexed to a single molecule. The resulting novel oligomeric metal chelate complexes have many properties which make them particularly advantageous, such as relatively low toxicity, beneficial imaging properties and distinctive biodistribution characteristics.

A direct relationship exists between the concentration of an X-ray attenuator and its efficacy in contrast enhancement. This concentration versus contrast effect relationship is not linear with respect to MRI contrast agents where a threshold concentration of the paramagnetic entity is required to affect the proton relaxation rates in a physiologic region that is being imaged and so enhance contrast. Beyond this threshold concentration, any further increase in concentration results in little improvement in contrast enhancement. Thus a primary benefit of the oligomeric polychelates for MR applications lies in the ability to lower the threshold dosage of contrast agent (and hence the toxicity) required for enhancement. The biodistribution and pharmacokinetic properties of the polychelates may also differ advantageously from those of monomeric chelate contrast agents.

As used herein, the term "oligomeric polychelant" refers to chelants capable of chelating more than one metal ion, i.e. comprising more than one chelating site, as compared for example to the monomeric "monochelants" such as DTPA or EDTA which have only one chelating site per molecule. The multiple chelating sites in the polychelants of the invention are capable of complexing metal ions, and in particular paramagnetic metal ions (e.g. of atomic number 21 to 29, 42, 44 and 57 to 71, especially 24 to 29 and 62 to 69), heavy metal ions (e.g. of atomic number 37 or more preferably 50 or more) and ions of radioactive metal isotopes.

For use in diagnostic imaging, radiotherapy or heavy metal detoxification, the polychelants of the invention are advantageously used to chelate lanthanides (e.g. La, Ce, Pr, Nd, Pm, Sm, ^{153}Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu) and other metal ions such as, for example, Mg, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu (e.g. ^{64}Cu or ^{67}Cu), Zn, Ga, Sr, Y, Zr, Tc, Ru, In, Hf, W, Re, Os, Pb and Bi, including isotopes and radioisotopes thereof, especially Eu^{3+}, Gd^{3+}, Dy^{3+}, Ho^{3+} and Yb^{3+}. Particularly preferred radioisotopes include ^{153}Sm, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{89}Sr, ^{88}Y, ^{90}Y, ^{99m}Tc, ^{97}Ru, ^{103}Ru, ^{111}In, ^{186}Re, ^{188}Re, ^{203}Pb, ^{211}Bi, ^{212}Bi, ^{213}Bi and ^{214}Bi.

Because the polychelants of the invention comprise a multiplicity of chelating sites, the chelate complexes formed therewith may include more than one metal ion. For MRI or X-ray and ultrasound applications the chelates of the inven-

tion preferably comprise, per molecule, two complexed paramagnetic metal ions or heavy metal ions respectively. In one generally preferred embodiment, the chelated metal ions are of the same element and isotope; however in other preferred embodiments the polychelant may be used to chelate ions of two different metal elements or isotopes. In this way, for example, the X-ray cross section of a contrast agent can be matched to the X-ray spectrum used for radiographic investigation by selecting a polychelate comprising ions of two different heavy metals.

Similarly, it is known that heavy metal chelate toxicity may be reduced by inclusion of chelated calcium or other relatively weak chelate complex forming ions within an MRI contrast medium (see WO-A-90/03804 of Salutar Inc and EP-A-270483 (Schering)) and one of the chelant sites in a polychelate according to the invention may be used to chelate calcium or other physiologically tolerable, weak complex forming metal ions.

The ability to incorporate a plurality of metal ions in a single molecule results in the polychelates according to the invention, on a molar basis, being able to exhibit greater response in *in vivo* applications such as magnetic resonance imaging, X-ray/CT, nuclear medicine, and the like. Similarly, in heavy metal detoxification each polychelant molecule or weak complex thereof will be capable of removing more than one toxic metal ion from the body, thus increasing the molar efficacy of the treatment.

Due to the increased number of chelation sites on the polychelant compounds of the invention compared to monochelants a lower molar dosage may be used to achieve the same level of metal chelation. Since chelate toxicity is dependent on factors such as the degree to which the chelated metal ion is released in vivo, the effects on plasma ion concentrations of the non-complexed or weakly complexed chelant sites, specific chemotoxic effects of the metal chelate complex and the number of particles (osmolality), this decreased dosage can result in a reduction in toxicity in view of, for example, decreased metal ion release, reduced unwanted plasma ion concentration distortion, decreased osmolality etc.

In addition, the relatively high molecular weights of the polychelant and polychelates of the invention as well as their ability to be coupled to functional substituents (such as plasma proteins, antibodies or antigens) allows selection of appropriate biodistribution characteristics and permits tissue or organ targetting, i.e. preferential delivery to such tissue material as tumours. This in turn will result in improved imaging characteristics, e.g. better selectivity, contrast/noise ratio, imaging time, and the like.

Additional benefits of the present invention will be apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

In illustrating the molecular structure of the oligomeric polychelants and polychelates of the invention, the macrocyclic chelant moieties will be designated most generally by the symbol "A". Such chelant moieties may be chosen from those known in the art to be capable of complexing metal ions, and include, for example, the residues of polyaminopolycarboxylic acids (PAPCAs) and derivatives thereof, e.g. 1,4,7,10-tetraazacyclododecanetetraacetic acid (DOTA), 1-oxa-4,7,10-triasacyclododecanetriacetic acid (OTTA) and 1,4,7,10-tetraasacyclododecanetriacetic acid (DO3A). Derivatives of such chelants, for example their amides and esters, especially optionally hydroxylated C_{1-18} alkyl-amides or -esters are also appropriate and often preferred chelants, as will be described in detail below.

Many PAPCAs are known and have been suggested in the literature for use for example as chelants in paramagnetic MRI contrast agents or as heavy metal detoxification agents. In this regard, besides those compounds mentioned above, particular reference may be had to the PAPCAs disclosed or discussed in EP-A-71564, EP-A-130934, DE-A-3401052, EP-A-230893, EP-A-232751, EP-A-292689, EP-A-255471, EP-A-287465, US-A-4687659, WO-A-89/06979 and WO-A-89/00557 and the documents referred to therein.

For sake of clarity, the symbol A is used herein to designate the chelant moieties whether chelated to a metal ion M or not, whether deprotonated (or otherwise ionized) or not.

The symbol "L" is used herein to designate the linker moiety XL'X.

An important aspect of the invention is that the chemical bond between each chelant moiety A and its adjacent linker moiety L comprises an amide or ester linkage with the carbonyl group adjacent the chelant moiety.

Thus the bonds A-L in the polychelant or polychelates of the invention will generally be of the formula

A'-CO-X-L'

where A'CO and L'X respectively are A and L and X is oxygen or a secondary, tertiary or ring nitrogen.

X is preferably attached to a carbon of L'.

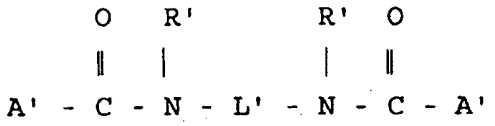
Where X is a secondary nitrogen, one or both (but preferably one) of the X-attached portions of L may serve to link the chelant moieties of the oligomer. Non-linking X-attached groups are preferably groups X^{111} R' where X^{111} is a bond, an oxygen or sulphur atom or a group NR^1 and R' is selected from hydrogen, hydrocarbon groups such as for example alkyl, cycloalkyl, alkenyl, alkynyl and aryl groups optionally substituted by hydroxyl, amine and carboxyl groups and derivatives thereof and other suitable groups; carbohydrate groups; peptide residues; polypeptides; proteins; and other

biomolecules.

The linker moiety in the compounds of the invention serves to link together the two chelant moieties, thereby holding together the multiple chelating site structure that is characteristic of the compounds of the invention. Besides filling this role as linker, or spacer, of chelant sites, the linker moiety can be so selected as to yield a product having other desired characteristics. Thus for example it is possible to increase hydrophilicity, lipophilicity or tissue specificity of the end product by attaching to or incorporating within the linker moiety groups which are hydrophilic, lipophilic or tissue targetting. To achieve a desired balance between overall molecular weight and number of chelant sites per molecule, the length or molecular weight of the linker moiety may be selected appropriately.

Moreover, for the end product to be readily characterized, i.e. for the different molecules within a given sample to be relatively uniform, readily characterizable precursors for the linker moiety may be used. The overall molecular weight of the linker moiety, excluding any pendant macromolecules or biomolecules will be less than 1000, most particularly less than 500 and especially less than 150. In order to achieve a relatively high chelated metal ion density within the polychelates of the invention, mid-chain linker moieties will preferably provide a chain of up to 22, preferably up to 12, especially up to 10 and particularly 3 to 8, atoms in length between the carbonyl carbons of the amide or ester bonds to adjacent chelant moieties. The terminal atoms of such chains will of course be oxygen or nitrogen, although preferably both will be nitrogen, and mid chain atoms will preferably be carbon although other mid chain atoms such as nitrogen, phosphorous, boron, silicon and oxygen may occur. Excluding terminal oxygens and nitrogens therefore, the linker moieties will preferably be optionally unsaturated, optionally substituted, optionally carbocyclic or heterocyclic ring containing, linear or branched hydrocarbon groups, e.g. oxa, aza, hydroxy, amino, carboxyl, cycloalkylene (e.g C_5 to C_7 cycloalkylene) or arylene (e.g. C_6 to C_{10} arylene) substituted alkylene, alkenylene or alkynylene groups.

It will frequently be useful to utilize di- or polyamino linker moieties L, as for example in structures of the form A—L—A, where the bonding is exemplified by the structure



where each R' is as defined above.

The amide linkages depicted above are particularly advantageous in that the carbonyl group being adjacent the chelant moiety is potentially able to contribute to the metal coordination effect and thereby increase the stability of the resultant complex. This carbonyl portion of the amide linkage may be derived from, for example, a carboxylate group in a precursor PAPCA. Such polychelants may be synthesized in high yields, for example using standard techniques e.g. as described below, from relatively inexpensive starting materials, such as PAPCAs and polyamine linker compounds, with minimal need for selective protection of functional groups on the chelants.

In one preferred embodiment of the invention, the linker moiety is a group $L''X_i$ where X is as hereinbefore defined, i is a positive integer, preferably 2, 3 or 4, and L'' is a branched or linear, substituted or unsubstituted, hydrocarbon group, such as an alkylene, cycloalkylene, alkenylene, alkynylene or arylene group, preferably containing from 1 to 20 carbons and most preferably 1 to 6 carbons, or a combination of two or more such groups or $L''X_i$ is a polyalkylamine residue (such as $-NH(CH_2CH_2NH-)_j$, j being preferably 1 to 20), or an aminopolyether or aminopolyalcohol residue (such as an aminopolyethylene-glycol residue) preferably containing from 4 to 20 carbons and most preferably 4 to 8 carbons, or an aminocarbohydrate residue, or an aminofatty acid residue or the residue of another compound capable of forming an amide or ester linkage with two chelant moieties (with any substitutent preferably being chosen to enhance solubility or biodistribution of the resultant compound, such as -OH, $-NH_2$ or $-CO_2H$, a peptide residue, a polypeptide or protein such as a plasma protein, antibody or antigen, or other suitable moiety).

The oligomeric polychelants and the chelate complexes of the invention include a wide variety of structures wherein two chelant moieties A are linked to each other through one linker moiety.

In one preferred embodiment, the chelant moieties A will be derived from or related to the same mono-chelant.

Preferred linker compounds useful for the production of the oligomeric compounds described herein include, but are not limited to, polyamino compounds such as the following

1,2-diaminoethane,
1,3-diaminopropane,
1,4-diaminobutane,
1,5-diamino-3-(2-aminoethyl)-pentane,
N,N'-dimethyl-1,2-diaminoethane,

N,N'-dimethyl-1,3-diaminopropane,
2-hydroxy-1,3-diaminopropane,
2-amino-1,3-diaminopropane,
2,3-diamino-1,4-butanediol,
1,4-diamino-2,3-butanediol,
1,4-diaminocyclohexane,
1,4-phenylenediamine, and especially
1,1,1-tris(aminomethyl)ethane,
2,2',2"-triaminotriethylamine,
tris-(aminomethyl)methane,
diethylenetriamine,
triethylenetetraamine,
1,3,5-triaminocyclohexane, and
1,3,5-phenylenetriamine.

Where X in L'X is oxygen, it is frequently preferable to choose a bulky, as for example a branched, L' in order to increase the stability of the resulting ester bond against hydrolysis. In this regard, preferred linker compounds include, but are not limited to, polyhydroxy compounds such as the following

2,2-dimethyl-1,3-propanediol,
tris(2-hydroxyethyl)amine,
1,1,1-tris(hydroxymethyl)ethane, and
tris(hydroxymethyl)aminomethane.

The synthetic methods described herein allow the use of linker compounds such as the foregoing to produce oligomeric polychelants of highly defined structure and size. By selecting linker moieties of specific structure, polychelant/polychelate compounds are produced that are relatively stable against hydrolysis in vivo as compared to protein or polypeptide based chelates. Moreover, the cost of starting materials useful in forming the linkages described is much lower than, for example, that of a homopolypeptide backbone.

In one preferred embodiment of the polychelates of the invention, the net negative charge on the chelant moieties balances or substantially balances the net positive electrical charge on the metal cations chelated by the polychelant whereby the net charge of the polychelate as a whole is low or even zero, so enabling low osmolality compositions of the polychelate to be prepared.

In a particularly preferred embodiment of the present invention, the polychelants comprise at least one chelant moiety that provides a net negative electrical charge sufficient to neutralize the net positive electrical charge on the metal cation associated with that chelant. This eliminates the need to have a salt-forming ion, as for example Na^+ or K^+, additionally associated with the chelant in order to achieve charge neutrality within that particular chelant metal (A--M) complex, and thereby beneficially decreases the osmolality of the subject compounds and lowers their toxicity. Most preferably, each A--M complex in the oligomeric polychelate will exhibit such charge neutrality.

Charge neutrality may be achieved by selecting as R a substantially non-ionizing substituent group. Suitable R-groups would therefore include those forming a stable amide or ester functionality, as for example where R is N-methylamino, N-methylglucamino, ethoxy, benzoxy, or another alkoxy group stable to hydrolysis under these conditions. Examples of suitable R-groups are disclosed in US-A-4687658 and 4687659.

This ability to select chelant moieties and substituent groups so as to form low ionic or non-ionic polychelates is a principle that is applicable also to other compounds of the present invention. In particular, it will frequently be advantageous to choose the specific individual monochelant such that the net formal charge on each chelant moiety within the oligomeric polychelant is the same.

It will also readily be seen in view of the foregoing description that the individual chelant moieties within the oligomeric polychelants of the invention may frequently allow substitution in one or more of a variety of positions. Where a choice of linkage or substitution positions is possible, the particular isomer selected may be dictated by considerations of toxicity, viscosity, solubility, synthetic ease, stability of ligand-metal association, or other considerations. The present invention provides techniques for achieving such varying isomers as will be discussed in more detail below.

Thus, viewed from a further aspect, the invention provides a process for the preparation of a polychelant according to the invention, said method comprising reacting one or more monochelant compounds or derivatives thereof having at least one reactive functional group with one linker compound having at least two functional groups capable of reacting with reactive groups of said monochelants and subsequently if required removing any protecting groups used.

In the process of the invention, the ratios of the quantities of the reagents used will generally correspond to the desired ratios of the chelant and linker moieties of the end product or of the intermediate product if oligomerization is

performed in stepwise fashion. The reaction can be performed stepwise or at one time and the product should be periodically sampled to ensure that the desired oligomer is being produced.

In one embodiment, the process of the invention comprises the steps of

(a) obtaining, from a polycarboxylate monochelant starting compound, optionally in carboxylate salt form, an activated polycarboxylate compound containing one or more reactive groups, e.g. imide, amide, anhydride or other activated carboxyl groups;
(b) forming an amide or ester linkage between said activated compound and a polyamine or polyol linking compound thereby to obtain a chelant-linker compound, e.g. using as said linking compound a compound comprising a body portion L' as herein defined and at least two reactive hydroxyl and/or amine groups;
(c) forming an amide or ester linkage between said chelant-linker compound and a second activated polycarboxylate compound to obtain an oligomeric polychelant.

In this process, one or more of the activated polycarboxylate compounds of steps (a) and (c) may be further substituted at one or more carboxyl moieties with a group of the form R, wherein R is as hereinbefore defined, e.g. a group NR'_2 or OR' where each R' is hydrogen, substituted or unsubstituted alkyl, cycloalkyl or an aromatic (with any substituting moiety being chosen from the group consisting of -OH, $-NH_2$ and $-CO_2H$), or a carbohydrate group, a peptide residue, polypeptide, or a protein.

In the process of the invention one or more of the reactive groups in the reagents, especially on the linking compound, may be protected during the linkage forming step or steps and then subsequently deprotected, e.g. to allow further build up of the oligomeric structure or to allow chelate formation.

The application of the oligomeric polychelants of this invention to medical diagnosis and/or therapy requires in many cases that they be chelated with an appropriate metal or metals. This may be readily accomplished by techniques known to the art (see for example EP-A-292689). Thus for example, the metal to be chelated can be added to water or another liquid medium in the form of an oxide or in the form of an inorganic or organic salt or weak chelate, e.g. a halide or acetate salt, and reacted with an appropriate amount of a polychelant according to the invention or a salt, anhydride or weak complex thereof. The polychelant or salt thereof can be added as an aqueous solution or as a suspension. Heating at temperatures as high as 100°C for periods up to 48 hours can be utilized depending on the form of the metal and the polychelant used, and their respective concentrations.

Some of the polychelates will be ionic and require counterions. For medical use such counterions should of course be physiologically acceptable. Suitable counterions are well known in the pharmaceutical field and include for example alkali and alkaline earth metal ions such as sodium, potassium, calcium and magnesium as well as organic cations and anions, e.g. ions of organic bases such as ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine and ions of amino acids or other naturally occurring physiologically tolerable acids. Such polychelate salts may be prepared for example by using a base (for example, an alkali metal hydroxide, meglumine, etc.) to neutralize the polychelates while they are still in solution. Neutral complexes, i.e. those complexes with no formal charge, may require the addition of dilute acid or base to maintain a pH near 7.0. Such neutral complexes are preferred over charged complexes as intravenously administered X-ray and NMR imaging agents because they provide solutions of greater physiologic tolerance due to their lower osmolality.

Thus viewed from another aspect the invention provides a process for producing polychelates according to the invention, said process comprising reacting a polychelant according to the invention, or a salt or weak complex thereof, in a liquid, preferably aqueous, medium with at least one metal compound, preferably an oxide or a compound soluble in water or an organic solvent, e.g. an alkanol, thereby to yield a polychelate containing two or more chelated metal ions per molecule.

Viewed from a further aspect the invention provides the use of a polychelant according to the invention or a salt or chelate thereof for the manufacture of a therapeutic or diagnostic agent for use for example in a method of a diagnostic imaging (e.g. X-ray imaging, MRI, ultrasound imaging, scintigraphy, etc), in radiotherapy or in heavy metal detoxification.

Viewed from a still further aspect the invention also provides a process for the preparation of a diagnostic or therapeutic agent which process comprises admixing a polychelant according to the invention, or a physiologically acceptable salt or chelate thereof, together with at least one pharmaceutical carrier or excipient.

Viewed from another aspect the invention provides a diagnostic or therapeutic composition, e.g. for use in a method of a diagnostic imaging (e.g. X-ray imaging, MRI, ultrasound imaging, scintigraphy, etc), in radiotherapy or in heavy metal detoxification, comprising a polychelant according to the invention or a physiologically acceptable salt or chelate thereof together with at least one pharmaceutical carrier or excipient.

The compositions according to the invention may have a variety of uses, particularly in diagnostic imaging, radiotherapy and heavy metal detoxification. The polychelant, or salt or chelate thereof, contained in the composition will of course be selected according to the desired end use. Thus compositions which are MRI contrast media will contain

chelates of the polychelant with at least one paramagnetic metal ion, preferably at least two such ions. Suitable paramagnetic metal ions have been discussed above but particular mention should be made in this regard to Eu, Ho, Gd, Dy, Mn, Cr and Fe, especially Gd(III), Mn(II) and Dy(III). For such use the paramagnetic metal species is preferably non-radioactive.

Compositions according to the invention which are X-ray or ultrasound contrast media will contain chelates of the polychelant with at least one heavy metal ion (of atomic number greater than 37, preferably greater than 50), preferably at least 2. The heavy metals may if desired be selected to match their X-ray cross-sections to the X-ray source to be used in imaging so as to optimise the contrast enhancement or alternatively the composition may advantageously contain polychelates of more than one heavy metal - either as a mixture of homopolychelates or as a heteropolychelate. Again suitable metals have been discussed above but particular mention may be made of Hf, La, Yb, Dy and Gd, especially Gd(III) and Dy(III). The heavy metal species will of course preferably be non-radioactive.

For use in scintigraphy and radiotherapy, the chelated metal species must of course be radioactive and any conventional complexable radioactive metal may be used, for example radioactive isotopes of Tc, Cu, In, Sm, Ru or Y. For radiotherapy, the polychelates with for example ^{67}Cu may be used.

For use in detoxification of heavy metals, the polychelant is preferably in salt form with a physiologically acceptable counterion, e.g. sodium, calcium, ammonium, zinc or meglumine.

Viewed from a still further aspect the invention provides a method of generating an image of a human or non-human, preferably mammalian, body said method comprising administering to said body a polychelate according to the invention or a physiologically acceptable salt thereof and generating an image, e.g. an MR, X-ray, ultrasound or scintigraphic image, of at least part of said body, e.g. after permitting sufficient time to elapse for the polychelate to distribute to the desired parts of said body.

Where the polychelate carries an overall charge it will conveniently be used in the form of a salt with a physiologically acceptable counterion, for example an ammonium, substituted ammonium, alkali metal or alkaline earth metal cation or an anion deriving from an inorganic or organic acid. In this regard, meglumine salts are particularly preferred.

The oligomeric polychelates of the invention are administered to patients for imaging in amounts sufficient to yield the desired contrast with the particular imaging technique. Generally dosages of from 0.001 to 5.0 mmoles of chelated contrast-producing ion per kilogram of patient bodyweight are effective to achieve adequate contrast enhancement. For most MRI applications preferred dosages of chelated imaging ion will be in the range from 0.02 to 1.2 mmoles/kg bodyweight while for X-ray applications dosages of from 0.5 to 1.5 mmoles/kg are generally effective to achieve satisfactory X-ray attenuation. Preferred dosages for most X-ray applications are from 0.8 to 1.2 mmoles of the chelated lanthanide or heavy metal/kg bodyweight.

The polychelants/polychelates of the present invention may be formulated with conventional pharmaceutical or veterinary aids, for example stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, etc., and may be in a form suitable for parenteral or enteral administration, for example injection or infusion or administration directly into a body cavity having an external escape duct, for example the gastrointestinal tract, the bladder or the uterus. Thus the compositions of the present invention may be in conventional pharmaceutical administration forms such as tablets, capsules, powders, solutions, suspensions, dispersions, syrups, suppositories etc.; however, solutions, suspensions and dispersions in physiologically acceptable carrier media, for example water for injections, will generally be preferred.

The compounds according to the invention may therefore be formulated for administration using physiologically acceptable carriers or excipients in a manner fully within the skill of the art. For example, the compounds, optionally with the addition of pharmaceutically acceptable excipients, may be suspended or dissolved in an aqueous medium, with the resulting solution or suspension then being sterilized. Suitable additives include, for example, physiologically biocompatible buffers (as for example, tromethamine hydrochloride), additions (e.g., 0.01 to 10 mole percent) of chelants (as for example, DTPA, DTPA-bisamide (e.g. 6-carboxymethyl-3,9-bis(carbamoylmethyl)-3,6,9-triazaundecanedioic acid) or non-complexed oligomeric polychelants) or calcium chelate complexes (as for example calcium DTPA, calcium DTPA-bisamide, NaCaDTPA-bisamide, calcium oligomeric polychelant or NaCa-oligomeric polychelant), or, optionally, additions (e.g., 1 to 50 mole percent) of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate and the like).

If the compounds are to be formulated in suspension form, e.g., in water or physiological saline for oral administration, a small amount of an insoluble polychelant or polychelate may be mixed with one or more of the inactive ingredients traditionally present in oral solutions and/or surfactants and/or aromatics for flavoring.

For MRI and for X-ray imaging of some portions of the body the most preferred mode for administering metal chelates as contrast agents is parenteral, e.g., intravenous administration. Parenterally administerable forms, e.g., intravenous solutions, should be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation or other adverse effects upon administration and thus the contrast medium should preferably be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride

Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 15th ed., Easton: Mack Publishing Co., pp. 1405-1412 and 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975). The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used for parenteral solutions, excipients and other additives which are compatible with the chelates and which will not interfere with the manufacture, storage or use of products.

The compositions of the invention may also, of course, be in concentrated or dried form for dilution prior to administration.

The present invention will now be illustrated further by the following non-limiting Examples. Examples 2-21 are comparative examples describing techniques which may be used analogously in preparing compounds of the invention. Other techniques which may be used in preparing the compounds of the invention can be found in the Examples of WO-A-91/05762, the contents of which are incorporated herein by reference.

Example 1

1,8-Bis[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-2,7-dioxo-3,6-diazaoctane (EthylDOTA Dimer)

(a) 1,8-Bis[4,7,10-tris(2-ethoxy-2-oxoethyl)-1,4,7,10-tetraazacyclododec-1-yl]-2,7-dioxo-3,6-diazaoctane (EthylDOTA-hexaethylester Dimer)

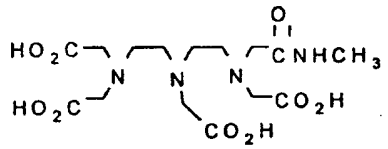
To a stirred solution of K^+DOTA-Triethylester (23.8 g, 0.0453 mol) in 500 mL of anhydrous tetrahydrofuran is added dicyclohexylcarbodiimide (9.33 g, 0.0453 mol) and 1-hydroxybenzotriazole (6.07 g, 0.0453 mol). The suspension is stirred for 15 minutes at ambient temperature and ethylenediamine (1.51 mL, 0.0226 mol) is added. After stirring an additional 24 hours at ambient temperature, the suspension is filtered and the solvents are evaporated. The residue is dissolved in 800 mL of ethyl acetate and is washed with 800 mL of saturated, aqueous sodium bicarbonate. Flash chromatography of the residue affords 18.0 g of EthylDOTA-hexaethylester dimer.

(b) 1,8-Bis[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-2,7-dioxo-3,6-diazaoctane (EthylDOTA Dimer)

To a stirred solution of EthylDOTA-hexaethylester dimer (15.0 g, 0.0163 mol) in 100 mL of tetrahydrofuran is added 200 mL of a 1 N sodium hydroxide solution. After stirring at ambient temperature for 4 hours, sufficient Bio-Rad AG50-X8 resin is added to the solution to adjust the pH to 2.2. The suspension is filtered and the filtrate is evaporated and lyophilized to provide the title product (11.5 g).

Example 2

5,8,11-Tris(carboxymethyl)-3-oxo-2,5,8,11-tetraazatridecan-13-oic Acid Monohydrate (DTPA-MMA • H_2O)

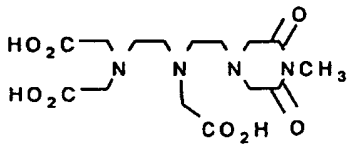


To a 12-L 3-neck round bottom flask equipped with mechanical stirrer, reflux condenser, thermometer, and nitrogen line was added DTPA (1.093 kg, 2.78 mol), anhydrous triethylamine (1.94 L, 13.9 mol), and anhydrous acetonitrile (3.9 L). The mechanically stirred mixture was heated to 60-65°C under nitrogen for 3 hours after which time virtually all solid dissolved. This solution was cooled to -30°C and isobutylchloroformate (361 mL, 2.78 mol) was added dropwise over 20 minutes while maintaining the temperature at -30°C. After stirring at -30°C for 1 hour, 40 wt % aqueous methylamine (2.39 L, 27.8 mol) was added over 5 minutes with stirring. The mixture was allowed to warm to 20-25°C. After 16 hours stirring was discontinued and the mixture was allowed to separate into two layers. The aqueous (lower) phase was removed by aspiration and concentrated by rotary evaporation (50°C, ca. 1 mm) to a viscous orange gum. The gum was dissolved in 3 L deionized (DI) water, the pH adjusted to 11.0-11.5 with 5 N NaOH, and the solution concentrated by rotary evaporation to a white solid. This step was repeated twice to hydrolyze DTPA-isobutyl ester by-products. The

solid was dissolved in 1 L DI water and adjusted to pH 6.5 with 12 M HCl. After cooling to 20°C, the solution was loaded onto a 30 x 100 cm column packed with 22 kg Dowex 1-X8 (acetate, 50-100 mesh). The material was eluted with 30 L DI water, 30 L of 1 N, 30 L of 2 N, 45 L of 3 N, and 45 L of 4 N acetic acid (elution by gravity at ca. 325 mL/min; monitored by UV at 254 nm). The product began eluting with late 2 N and continued through 4 N acetic acid. Fractions (4 L each) were combined on the basis of ^{1}H NMR, concentrated by rotary evaporation, and repeatedly reconcentrated with several portions of DI water until acetate free amide was obtained. Lyophilization (10 μ, 14 hours) of this material provided 203 g (17% yield) DTPA-MMA • H_2O. ^{1}H NMR (250 MHz, D_2O): δ 2.55 (s, 3H), δ 2.97-3.05 (m, 4H), δ 3.19 (t, 2H, J = 6.0 Hz), δ 3.27 (t, 2H, J = 6.0 Hz), δ 3.46 (s, 2H), δ 3.65 (s, 2H), δ 3.75 (s, 6H).

Example 3

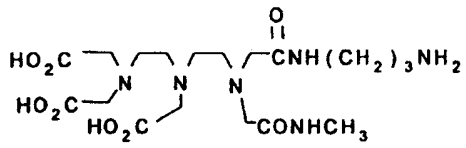
N-[2-[Bis(carboxymethyl)amino]ethyl]-N-[2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl]glycine Monohydrate (DTPA-MMI • H_2O)



To a 500 mL round bottom flask containing a magnetic stirrer was added DTPA-MMA • H_2O (15.0 g, 35.3 mmol) and glacial acetic acid (250 mL). The flask was fitted with a condenser, and the stirred solution was warmed to 80°C under nitrogen in an oil bath. After 18 hours the reaction mixture was cooled to room temperature, concentrated by rotary evaporation and further dried by high vacuum to an orange yellow solid. The solid was dissolved in 50-100 mL DI water and loaded onto a 14 x 2.5 inch (35.6 x 6.4 cm) column packed with Bio-Rad AG1-X8 (acetate, 100-200 mesh). The imide was eluted with 1.0 L DI water followed by 1.0 L each of 1 N, 2 N, 3 N and 4 N acetic acid under nitrogen pressure. The product began eluting with early 2 N through early 4 N acetic acid. Fractions (250-500 mL) were combined on the basis of purity and concentrated by rotary evaporation, and further dried by high vacuum to give 10.95 g (80% yield) DTPA-MMI • H_2O. ^{1}H NMR (250 MHz, D_2O): δ 2.81 (t, 3H, J = 5.4 Hz), δ 2.88(s, 3H), δ 3.14 (t, 2H, J = 5.4 Hz), δ 3.27-3.32 (m, 4H), δ 3.48 (s, 4H), δ 3.55 (s, 4H), δ 3.74 (s, 6H).

Example 4

15-Amino-3,6-bis(carboxymethyl)-9-[2-(methylamino)-2-oxoethyl-11-oxo-3,6,9,12-tetraazapentadecanoic Acid Monohydrochloride Monohydrate (DTPA-MA-APA • HCl • H_2O)

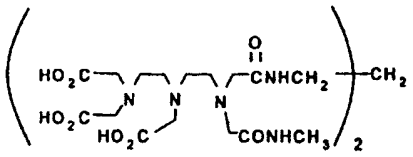


To a 50 mL round bottom flask equipped with magnetic stir bar was added DTPA-MMI • H_2O (4.15 g, 10.21 mmol), triethylamine (4.3 mL, 3.0 eq), and methanol (15 mL). The solid dissolved after 5-10 minutes and the flask, under nitrogen, was placed in an ice bath at 5-10°C and 1,3-diaminopropane (10.2 mL, 12.0 eq) was added in one portion. After 5 minutes the flask was removed from the ice bath and the mixture was stirred for 17 hours at ambient temperature. The solution was concentrated by rotary evaporation to an oily residue which was then dissolved in 25 mL DI water, adjusted to pH 11.5 (5N NaOH), reconcentrated to 10-15 mL, and applied to a 4 x 2 inch (10.2 x 5.1 cm) column packed with Bio-Rad AG1-X8 (acetate, 100-200 mesh). The amide was eluted with 300 mL DI water and 600 mL 1 N acetic acid. The

product was eluted with 1 N acetic acid. Fractions (125-250 mL) were combined on the basis of purity, concentrated by rotary evaporation, and further dried under high vacuum to a white solid residue. This solid was dissolved in 25 mL DI water, pH adjusted to 1.8 using 1 N HCl (8.9 mL, 1.0 eq), and concentrated to dryness. The residue was dissolved in 25 mL methanol and concentrated to dryness to afford 4.64 g (88% yield) DTPA-MA-APA • HCl • H_2O. ^1H NMR (250 MHz, D_2O): δ 1.66 (d, 2H, J = 7.2 Hz), δ 2.53(s, 3H), δ 2.78 (t, 2H, J = 7.5 Hz), δ 2.98-3.18 (m, 6H), δ 3.23 (t, 2H, J = 5.5 Hz), δ 3.36 (t, 2H, J = 5.6 Hz), δ 3.44 (s, 2H), δ 3.48 (s, 2H), δ 3.57 (s, 2H), δ 3.72 (s, 4H).

Example 5

3,6,22,25-Tetrakis(carboxymethyl)-9,19-bis[2-(methylamino)-2-oxoethyl]-11,17-dioxo-3,6,9,12,16,19,22,25-octaaza-heptacosanedioic Acid Dihydrate (PropylDTPA-(9,19)BMA-APA • $2H_2O$ dimer)

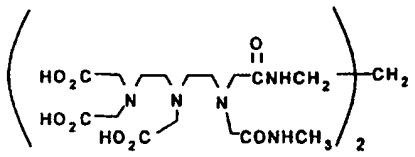


A 25 mL round bottom flask equipped with magnetic stir bar and nitrogen line was charged with DTPA-mono(methyl-propylamine)amide HCl • H_2O (0.57 g, 1.1 mmol) and DMSO (2.0 mL). The solid was dissolved with magnetic stirring and anhydrous 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1.1 mL, 8.8 mmol) was added followed by 0.25 g 4 Å molecular sieves (2-3 μm powder). To the stirring slurry was added DTPA-mono(methylimide) (0.43 g, 1.10 mmol). The mixture was warmed (ca. 35°C) and then allowed to stir at ambient temperature under nitrogen. After 88 hours the mixture was quenched with 1,3-diaminopropane (1.1 mL, 12.0 eq), stirred 1 hour, diluted with 10 mL methanol and vacuum filtered through a 1/4" (0.64 cm) celite bed (medium fritted glass funnel) into a 250 mL round bottom flask containing stirred 1 N HCl (8.8 mL). The celite bed was washed with methanol (3 x 5 mL) and the combined filtrates were concentrated by rotary evaporation to near dryness. The oily residue was dissolved in 25 mL DI water, pH adjusted to 11.5 (5 N NaOH), and concentrated by rotary evaporation. Following repeated reconcentration from DI water (2 x 25 ml), the residue was dissolved in 10 mL DI water, pH adjusted to 8.0 (5 N HCl), concentrated to 5-10 mL volume and applied to a 1 x 7" (2.5 x 17.8 cm) column bed of Bio-Rad AGI-X8 (acetate, 100-200 mesh). The dimer was eluted with 100 mL DI water, followed by 100 mL of 1 N, 2 N, 3 N, and 4 N acetic acid respectively. The product eluted with late 2 N through 3 N acetic acid. Fractions (50-100 mL) were combined on the basis of purity, concentrated by rotary evaporation, reconcentrated repeatedly from DI water (6 x 25 ml), and lyophilized (10μ, 14hours) to afford 0.18 g (19% yield) PropylDTPA-(9,19)BMA • $2H_2O$ dimer. ^1H NMR (250 MHz, D_2O): δ 1.54 (p, 1H, J = 6.4 Hz), δ 2.56 (s, 3H), δ 3.00-3.15 (m, 6H), δ 3.23 (t, 2H, J = 5.4 Hz), δ 3.36 (t, 2H, J = 5.9 Hz), δ 3.52 (s, 4H), δ 3.57 (s, 2H), δ 3.73 (s, 4H).

product was eluted with 1 N acetic acid. Fractions (125-250 mL) were combined on the basis of purity, concentrated by rotary evaporation, and further dried under high vacuum to a white solid residue. This solid was dissolved in 25 mL DI water, pH adjusted to 1.8 using 1 N HCl (8.9 mL, 1.0 eq), and concentrated to dryness. The residue was dissolved in 25 mL methanol and concentrated to dryness to afford 4.64 g (88% yield) DTPA-MA-APA • HCl • H_2O. ^1H NMR (250 MHz, D_2O): δ 1.66 (d, 2H, J = 7.2 Hz), δ 2.53(s, 3H), δ 2.78 (t, 2H, J = 7.5 Hz), δ 2.98-3.18 (m, 6H), δ 3.23 (t, 2H, J = 5.5 Hz), δ 3.36 (t, 2H, J = 5.6 Hz), δ 3.44 (s, 2H), δ 3.48 (s, 2H), δ 3.57 (s, 2H), δ 3.72 (s, 4H).

Example 5

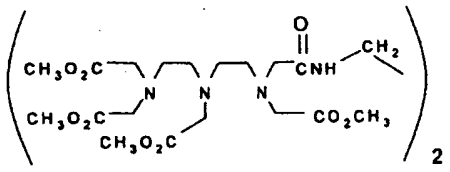
3,6,22,25-Tetrakis(carboxymethyl)-9,19-bis[2-(methylamino)-2-oxoethyl]-11,17-dioxo-3,6,9,12,16,19,22,25-octaaza-heptacosanedioic Acid Dihydrate (PropylDTPA-(9,19)BMA-APA • $2H_2O$ dimer)



A 25 mL round bottom flask equipped with magnetic stir bar and nitrogen line was charged with DTPA-mono(methyl-propylamine)amide HCl • H_2O (0.57 g, 1.1 mmol) and DMSO (2.0 mL). The solid was dissolved with magnetic stirring and anhydrous 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1.1 mL, 8.8 mmol) was added followed by 0.25 g 4 Å molecular sieves (2-3 μm powder). To the stirring slurry was added DTPA-mono(methylimide) (0.43 g, 1.10 mmol). The mixture was warmed (ca. 35°C) and then allowed to stir at ambient temperature under nitrogen. After 88 hours the mixture was quenched with 1,3-diaminopropane (1.1 mL, 12.0 eq), stirred 1 hour, diluted with 10 mL methanol and vacuum filtered through a 1/4" (0.64 cm) celite bed (medium fritted glass funnel) into a 250 mL round bottom flask containing stirred 1 N HCl (8.8 mL). The celite bed was washed with methanol (3 x 5 mL) and the combined filtrates were concentrated by rotary evaporation to near dryness. The oily residue was dissolved in 25 mL DI water, pH adjusted to 11.5 (5 N NaOH), and concentrated by rotary evaporation. Following repeated reconcentration from DI water (2 x 25 ml), the residue was dissolved in 10 mL DI water, pH adjusted to 8.0 (5 N HCl), concentrated to 5-10 mL volume and applied to a 1 x 7" (2.5 x 17.8 cm) column bed of Bio-Rad AGI-X8 (acetate, 100-200 mesh). The dimer was eluted with 100 mL DI water, followed by 100 mL of 1 N, 2 N, 3 N, and 4 N acetic acid respectively. The product eluted with late 2 N through 3 N acetic acid. Fractions (50-100 mL) were combined on the basis of purity, concentrated by rotary evaporation, reconcentrated repeatedly from DI water (6 x 25 ml), and lyophilized (10μ, 14hours) to afford 0.18 g (19% yield) PropylDTPA-(9,19)BMA • $2H_2O$ dimer. ^1H NMR (250 MHz, D_2O): δ 1.54 (p, 1H, J = 6.4 Hz), δ 2.56 (s, 3H), δ 3.00-3.15 (m, 6H), δ 3.23 (t, 2H, J = 5.4 Hz), δ 3.36 (t, 2H, J = 5.9 Hz), δ 3.52 (s, 4H), δ 3.57 (s, 2H), δ 3.73 (s, 4H).

Example 6

Dimethyl-3,6,9,18,21,24-hexakis(2-methoxy-2-oxoethyl)-11,16-dioxo-3,6,9,12,15,18,21,24-octaazahexacosanedioate (DTPA-Octaester Dimer)



(a) N,N-Bis(2-[bis(2-methoxy-2-oxoethyl) amino]ethyl]glycine methyl ester (DTPA-PMester)

To a stirred suspension of diethylenetriaminepentaacetic acid (100 g, 0.254 mol) in 1 L of absolute methanol was added trimethylorthoformate (200 mL, 1.83 mol). Anhydrous hydrogen chloride was bubbled in at a vigorous rate until the solution began to boil (5-10 minutes). The solution was allowed to boil for 3 hours without using a reflux condenser, and then cooled. Evaporation of the solvents afforded an oil which was diluted with 1 L of saturated, aqueous sodium bicarbonate and extracted with two 400-mL portions of ether. The combined extracts were dried ($MgSO_4$), filtered and evaporated to give 93.0 g (79% yield) of DTPA-PMester as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 2.65-2.85 (m, 8H), δ 3.24 (s, 2H), δ 3.32-3.47 (m, 8H), δ 3.54 (s, 3H), δ 3.65 (s, 12H).

(b) N-[2-[Bis(2-methoxy-2-oxoethyl)amino]ethyl]-N-[2-[(carboxymethyl)(2-methoxy-2-oxoethyl)amino]ethyl]-glycine methyl ester, potassium salt (K^+DTPA-TMester)

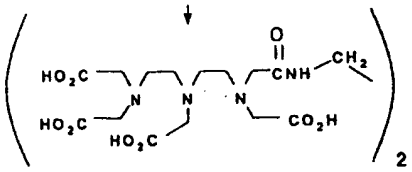
To a stirred solution of DTPA-PMester (93.0 g, 0.20 mol) in 200 mL of absolute methanol was added a solution of 87.8% potassium hydroxide pellets (12.8 g, 0.20 mol) in 50 mL of absolute methanol. The solution was stirred for 15 hours at ambient temperature and the solvent was evaporated. Flash chromatography (SiO_2, 0-30% methanol progression in chloroform) gave K^+DTPA-TMester (43.8 g, 45% yield) as a colorless oil. R_f 0.35 (15% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.74 (s, 6H), δ 2.85 (m, 2H), δ 3.35 (s, 2H), δ 3.45 (s, 2H), δ 3.49 (s, 2H), δ 3.53 (s, 4H), δ 3.66 (s, 12H).

(c) Dimethyl-3,6,9,18,21,24-hexakis(2-methoxy-2-oxoethyl)-11,16-dioxo-3,6,9,12,15,18,21,24-octaazahexacosanedioate (DTPA-Octaester Dimer)

To a stirred solution of K^+DTPA-TMester (43.8 g, 0.0898 mol) in 800 mL anhydrous tetrahydrofuran was added dicyclohexylcarbodiimide (18.5 g, 0.0898 mol) and 1-hydroxybenzotriazole (12.1 g, 0.0898 mol). The suspension was stirred for 15 minutes at ambient temperature and ethylenediamine (3.0 mL, 0.0449 mol) was added. After stirring an additional 18 hours at ambient temperature, the suspension was filtered and the solvents were evaporated. The residue was dissolved in 800 mL of ethyl acetate and washed with 800 mL of saturated, aqueous sodium bicarbonate The organic layer was separated, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (SiO_2, 0-5% methanol progression in chloroform) of the residue gave the product (37.2 g, 90% yield) as a clear, light yellow oil. R_f 0.75 (10% MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.60-2.85 (m, 16H), δ 3.22 (s, 4H), δ 3.34 (t, J = 2.5 Hz, 4H), δ 3.41 (s, 8H), δ 3.53 (s, 8H), δ 3.64 (s, 24H), δ 8.00 (br s, 2H).

Example 7

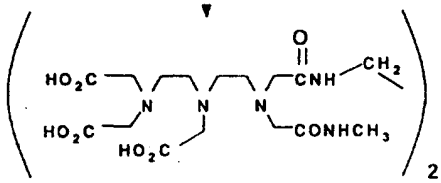
3,6,9,18,21,24-Hexakis(carboxymethyl)-11,16-dioxo-3,6,9,12,15,18,21,24-octaazahexacosanedioic Acid (DTPA-Octaacid Dimer)



To a stirred solution of DTPA-Octaester dimer (18.3 g, 0.0198 mol) in 100 mL of tetrahydrofuran was added 300 mL of a 1 N sodium hydroxide solution. After stirring at ambient temperature for 4 hours, sufficient Bio Rad AG50-X8 resin (100-200 mesh) was added to adjust the pH of the solution to 3.2. The suspension was filtered and the filtrate was evaporated and lyophilized (10 μ, 16 hours) to provide the product (14.5 g, 90% yield) as a hygroscopic, light yellow solid of sufficient purity for use in subsequent reactions. ^{1}H NMR (D_2O): δ 2.90-3.10 (m, 8H), δ 3.12-3.32 (m, 12H), δ 3.46 (s, 4H), δ 3.66 (s, 4H), δ 3.75 (s, 12H).

Example 8a

3,6,21,24-Tetrakis(carboxymethyl)-9,18-bis[2-(methylamino)-2-oxoethyl]-11,16-dioxo-3,6,9,12,15,18,21,24-octaaza-hexacosanedioic Acid (EthylDTPA-(9,18)BMA Dimer)



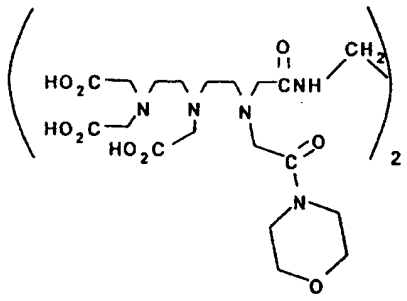
A suspension of DTPA-Octaacid dimer (0.202 g, 0.25 mmol) in 5 mL of glacial acetic acid was heated to 90°C for 24 hours. The solution was cooled, filtered and evaporated. Then 5 mL of water was added and the solution was evaporated. This was repeated to remove the last traces of acetic acid. The residue, the bisimide DTPA dimer, was dissolved in 10 mL of 40% aqueous methylamine and stirred at ambient temperature for 1 hour. The solution was evaporated and the residue was purified on Bio-Rad AG1-X8 resin eluting with a 0-4 M acetic acid progression.

The product was evaporated from water three times to remove acetic acid and lyophilized (10 μ, 14 hours) to afford the pure product as an off-white solid. ^{1}H NMR (D_2O): δ 2.55 (s, 6H), δ 3.00-3.12 (m, 8H), δ 3.17 (s, 4H), δ 3.25 (t, J = 5.0 Hz, 4H), δ 3.38 (t, J = 5.0 Hz, 4H), δ 3.47 (s, 4H), δ 3.48 (s, 4H), δ 3.57 (s, 4H), δ 3.71 (s, 8H); FAB mass spectrum, m/z: 837 (MH^+), 859 (MNa^+).

Further chelates can be produced analogously to Examples 6 to 8 by the same general scheme in which two or more eqivalents of a polycarboxyl-substituted chelant salt compound (i.e. a polycarboxyl chelant comprising substantially non-ionizing, non-salt substituted groups on fewer than all of its carboxyl moieties and a salt-forming cation on at least one, and preferably only one, carboxylate moiety) are reacted with a polyamino linker compound to form a polycarboxyl-substituted polychelant. One or more of the substantially non-ionizing substituent groups may thereafter be removed and optionally replaced with an alternate substituent group in one or more positions.

Example 8b

3,6,21,24-Tekrakis(carboxymethyl)-9,18-bis [4-(morpholino)-2-oxoethyl]-11,16-dioxo-3,6,9,12,15,18,21,24-octaaza-hexacosanedioic Acid (EthylDTPA-(9,18)BMO Dimer)



A suspension of DTPA-Octaacid dimer (0.202 g, 0.25 mmol) in 5 mL of galcial acetic acid is heated to 90°C for 24 hours. The solution is cooled, filtered and evaporated. This is repeated to remove the last traces of acetic acid. The residue, the bis-imide DTPA dimer, is dissolved in 10 mL of morpholine and stirred at ambient temperature for 24 hours. The solution is evaporated and the residue is purified by ion-exchange chromatography followed by lyophilization to afford the title compound.

Example 9

6,9,18,21-Tetrakis(carboxymethyl)-3,24-bis [2-(methylamino)-2-oxoethyl]-11,16-dioxo-3,6,9,12,15,18,21,24-octaaza-hexacosanedioic Acid (EthylDTPA-(3,24)BMA Dimer)

To a stirred solution of DTPA-MMA • H_2O (1.0 g, 2.35 mmol) in 30 mL of anhydrous pyridine at 0°C was added 1,3-dicyclohexylcarbodiimide (DCC) (1.069 g, 5.15 mmol). The ice bath was removed and the mixture allowed to stir for 4 hours at ambient temperature after which time ethylenediamine (78.8 µL, 1.17 mmol) was added. After stirring for 24 hours at ambient temperature, the mixture was stripped to dryness, 10 mL of H_2O was added, and the dicyclohexylurea (DCU) precipitate was removed by filtration. After adjusting the pH to 9.0 with 1 N NaOH, the solution was applied to a column of AG1-X8 (100-200 mesh, acetate) resin. The product was eluted with 1 N acetic acid to yield 0.320 g (33% yield) of the title dimer as a pale yellow solid after acetic acid removal followed by lyophilization. ^1H NMR (D_2O): δ 2.57 (s, 6H), δ 3.15-3.45 (m, 20H), δ 3.50-3.70 (m, 20H); FAB mass spectrum, m/z: 837 (MH^+).

Example 10

6,9,20,23-Tetrakis(carboxymethyl)-3,26-bis [2-(methylamino)-2-oxoethyl]-11,18-dioxo-3,6,9,12,17,20,23,26-octaaza-octacosanedioic Acid (ButylDTPA-(3,26)BMA Dimer)

To a stirred solution of DTPA-MMA • 0.43H_2O (1.00 g, 2.41 mmol) in 25 mL of anhydrous pyridine was added 1,4-diaminobutane (121 µL, 1.205 mmol). The now cloudy solution was cooled to ice bath temperature and DCC (0.547 g, 2.65 mmol) was added at once. The mixture was stirred for 24 hours at room temperature, stripped to dryness, diluted with 10 mL of water, and the DCU precipitate was removed by filtration. After adjusting the pH from 3.4 to 8.9 with 1 N NaOH, the solution was applied to AG1-X8 (100-200 mesh, acetate) resin, and eluted with 1N acetic acid. The pure fractions were combined to give 0.649 g (62% yield) of the title dimer as a white solid after acetic acid removal and lyophilization. ^1H NMR (D_2O): δ 1.28 (br s, 4H), δ 2.52 (s, 6H), δ 2.85-3.20 (m, 20H), δ 3.45-3.65 (m, 20H); FAB mass spectrum, m/z: 865 (MH^+).

Example 11

6,9,18,21-Tetrakis(carboxymethyl)-12,15-dimethyl-3,24-bis[2-(methylamino)-2-oxoethyl]-11,16-dioxo-3,6,9,12,15,18,21,24-octaazahexacosanedioic Acid (N,N'-dimethylethylDTPA-(3,24)BMA Dimer)

To a stirred solution of DTPA-MMA • 0.43 H_2O (1.0 g, 2.413 mmol) in 25 mL of anhydrous pyridine was added N,N'-dimethylethylenediamine (128 µL, 1.206 mmol). The cloudy mixture was cooled to ice bath temperature and DCC (0.548 g, 2.654 mmol) was added at once. After stirring for 24 hours at room temperature, the mixture was stripped to dryness, 10 mL of water was added, and the DCU precipitate was removed by filtration. After adjusting the pH to 8.9 with 1 N NaOH, the solution was applied to AG1-X8 (100-200 mesh, acetate) resin, and eluted with 1 N acetic acid to yield 0.516 g (49% yield) of the title dimer as a white solid after acetic acid removal and lyophilization. ^{1}H NMR (D_2O): δ 2.56 (s, 6H), δ 2.80 (s, 6H), δ 3.0-3.6 (m, 36H), δ 4.15 (s, 4H); FAB mass spectrum, m/z: 865 (MH^+).

Example 12

6,9,19,22-Tetrakis(carboxymethyl)-3,25-bis[2-(methylamino)-2-oxoethyl]-11,17-dioxo-3,6,9,12,16,19,22,25-octaaza-heptacosanedioic Acid (PropylDTPA-(3,25)BMA Dimer)

To a stirred solution of DTPA-MMA • 0.6 H_2O (11.61 g, 0.0278 mol) in 650 mL of anhydrous pyridine was added 1,3-diaminopropane (1.030 g, 0.0139 mol). The cloudy mixture was cooled to ice bath temperature and DCC (8.60 g, 0.0417 mol) was added in one portion. After stirring for 20 minutes, the ice bath was removed and the mixture stirred for 48 hours at ambient temperature. The mixture was stripped to dryness, 100 mL of water was added, and the pH adjusted from pH 3.3 to pH 9.0 with 5 N NaOH. DCU precipitate was removed by filtration and the solution was applied to AG1-X8 (100-200 mesh, acetate) resin. After three column volumes of water, the dimer product was eluted with 1 N acetic acid. The pure fractions were combined to give 5.55 g (47% yield) of the title product after reconcentration three times with water followed by lyophilization. ^{1}H NMR (D_2O): δ 1.5 (br t, J = 9.5 Hz, 4H), δ 2.49 (s, 6H), δ 2.80-3.20 (m, 20H), δ 3.45-3.60 (m, 20H); FAB mass spectrum, m/z: 851 (MH^+).

Example 13

6,9,19,22-Tetrakis(carboxymethyl)-14-hydroxy-3,25-bis[2-(methylamino)-2-oxoethyl]-11,17-dioxo-3,6,9,12,16,19,22,25-octaazaheptacosanedioic Acid (HOpropylDTPA-(3,25)BMA Dimer)

To a stirred solution of DTPA-MMA • H_2O (1.00 g, 2.35 mmol) in 50 mL of anhydrous pyridine at 0°C was added DCC (1.069 g, 5.15 mmol). The ice bath was removed and the mixture stirred for 3 hours at ambient temperature and 2-hydroxy-1,3-diaminopropane (0.106 g, 1.178 mmol) was added. After stirring for 24 hours at ambient temperature, the mixture was stripped to dryness, 10 mL of water added, and the DCU precipitate removed by filtration. After adjusting the pH from pH 3.4 to pH 9.0 with 1 N NaOH, the solution was applied to AG1-X8 (100-200 mesh, acetate) resin, and the product was eluted with 1 N acetic acid to yield 0.185 g (18% yield) of the title product as a pale yellow solid after HOAc removal followed by lyophilization. ^{1}H NMR (D_2O): δ 2.49 (s, 6H), δ 2.95-3.15 (m, 20H), δ 3.40-3.70 (m, 20H); FAB mass spectrum, m/z: 867 (MH^+).

Example 14

6,9,19,22-Tetrakis(carboxymethyl)-3,26-bis [2-[(2,3-dihydroxypropylamino)-2-oxoethyl]-11,17-dioxo-3,6,9,12,16,19,22,25-octaazaheptacosanedioic Acid (PropylDTPA-(3,25)APD Dimer)

To a stirred solution of DTPA-MAPD • 1H_2O (0.40 g, 0.825 mmol) in 25 mL of anhydrous pyridine at 0°C was added 1,3-diaminopropane (34 µL, 0.412 mmol). The solution was cooled and DCC (0.187 g, 0.906 mmol) was added. The mixture was stirred for 48 hours at ambient temperature, stripped to dryness, diluted with 10 mL of water, and the DCU removed by filtration. After adjusting the mixture from pH 3.8 to pH 8.9 with 1 N NaOH, the solution was applied to AG1-X8 (100-200 mesh, acetate) resin and eluted with 1 N acetic acid. The pure fractions were combined to give 0.040 g (10% yield) of the title dimer as an oily solid. ^{1}H NMR (D_2O): δ 1.55 (br t, 2H), δ 2.9-3.7 (m, 50H).

The DTPA-mono(2,3-hydroxypropylamide) chelant (DTPA-MAPD) used in Example 13 was prepared according to the method of Example 14. Other synthetic methods known to the art may be used to prepare substituted (e.g., amidated or esterified) monomeric chelants that are likewise useful in the synthesis of oligomeric polychelants according to the methods of, for instance, Examples 8-13.

Polychelants according to the invention can be produced by procedures analogous to those of Examples 9 to 14

using different monochelant and polyamino linker compound starting materials.

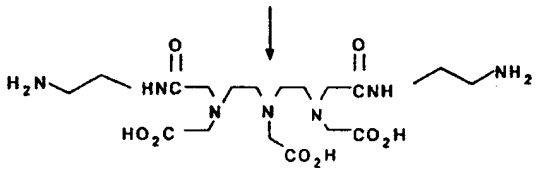
Example 15

3,6,9-Tris(carboxymethyl)-14-15-dihydroxy-11-oxo-3,6,9,12-tetraazapentadecanoic Acid (DTPA-MAPD)

A suspension of DTPA (1.0 g, 2.5 mmol) in 30 mL of DMSO containing triethylamine (1.77 mL, 12.7 mmol) was refluxed until solubilized. The solution was cooled to ambient temperature and 3-amino-1,2-propanediol (0.243 g, 267 mmol) was added, followed by DCC (0.543 g, 2.67 mmol). After stirring for 24 hours, the mixture was stripped to dryness, 10 mL of water was added, and the DCU was removed by filtration. After adjusting the pH from pH 2.9 to pH 8.0 with 1 N NaOH, the solution was applied to AG1-X8, acetate resin. The product was eluted with 1 N acetic acid. The pure fractions were combined to give 0.409 g (34% yield) of the title compound as a white solid after acetic acid removal and lyophilization. ^{1}H NMR (D_2O): δ 2.95-3.40 (m, 12H), δ 3.47 (s, 7H), δ 3.55-3.80 (m 9H); FAB mass spectrum, m/z: 467 (MH^+).

Example 16

14-Amino-3-[2-[(2-aminoethyl)amino]-2-oxoethyl]-6,9-bis(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic Acid Dihydrate (DTPA-B(AE)A • $2H_2O$)



(a) 1,1-Dimethylethyl(2-aminoethyl)carbamate ((tBA)EA)

A 250 mL round bottom flask equipped with magnetic stir bar, addition funnel, and nitrogen line was charged with ethylenediamine (43 mL, 0.65 mol) and chloroform (75 mL). To the stirred solution, cooled in an ice/methanol bath, was added di-t-butyl dicarbonate (21.8g, 0.10 mol) in 30 mL chloroform dropwise over one hour. The reaction mixture was stirred 18 hours at ambient temperature, filtered and concentrated by rotary evaporation to a clear oil. Repeated concentration from toluene (5 x 50 mL) provided 17 g of a colorless oil. Vacuum distillation of this oil (88-89°C, ca. 3 mm) gave 12.1 g (76% yield) (t-BA)EA. ^{1}H NMR (250 MHz, CD_3Cl): δ 1.12 (s, 2H), δ 1.39 (s, 9H), δ 2.74 (t, 2H, J = 5.9 Hz), δ 3.11 (q, 2H, J = 5.8 Hz), δ 4.97 (s, 1H).

(b) Bis(1,1-dimethylethyl)-8,11,14-tris(carboxymethyl)-6,16-dioxo-2,5,8,11,14,17,20-heptaazaheneicosanedioate (DTPA-B(tBA)EA)

A 500 mL round bottom flask equipped with magnetic stir bar and nitrogen line was charged with (tBA)EA (12.08 g, 75.42 mmol), triethylamine (15.0 mL, 107.7 mmol), and acetonitrile (200 mL). To the stirred solution was added DTPA dianhydride (12.83 g, 75.42 mmol) in one portion followed by acetonitrile (50 mL). After 15 minutes the white suspension became a colorless solution. The flask was fitted with a condenser and warmed under nitrogen in an oil bath at 50°C. After 90 hours the reaction mixture was concentrated by rotary evaporation to an off-white solid. This solid was dissolved in 150 mL DI water and concentrated by rotary evaporation to a dry solid. Residual triethylamine was removed by redissolving the solid in 150 mL DI water, adjusting the pH to 10.5 (5 N NaOH), and concentrating by rotary evaporation. ^{1}H NMR (250 MHz, D_2O): δ 1.00 (t, 8H, J = 7.0 Hz), δ 1.14 (s, 18H), δ 2.86-3.00 (m, 13.4H), δ 3.06 (s, 8H), δ 3.17 (s, 4H), δ 3.32 (s, 4H), δ 3.46 (s, 2H).

(c) 14-Amino-3-[2-[(2-aminoethyl)amino]-2-oxoethyl]-6,9-bis(carboxymethyl)-11-oxo-3,6,9,12-tetraazatetradecanoic Acid Dihydrate (DTPA-B(AE)A)

The DTPA-B(tBA)EA prepared above was dissolved in 110 mL DI water, adjusted to pH 7 (5N HCl), and cooled in

an ice bath. To the cool stirred solution was added concentrated HCl (39 mL) in one portion. The mixture was stirred 10 minutes in the ice bath then for 2 hours at ambient temperature. The solution was then cooled in an ice bath, titrated to pH 7 (50% NaOH), and concentrated by rotary evaporation to a dry solid (50 g). A portion of solid NaCl was removed from this material by suspending the solid in 50 mL DI water and vacuum filtering through a medium fritted glass funnel. The filtrate was adjusted to pH 2.5 (5N HCl), concentrated to a 50 mL suspension, and vacuum filtered through a coarse fritted glass funnel to remove additional solid NaCl. The filtrate was loaded onto a 9.5 x 2.0" (24.1 x 5.1 cm) column bed of Bio-Rad AG50-X8 (H^+, 200-400 mesh). The column was eluted under nitrogen pressure with 0.75 L DI water followed by 1.25 L of 2 N ammonium hydroxide. The product eluted with 2 N ammonium hydroxide. The UV active fraction was concentrated by rotary evaporation to an oily residue. The residue was dissolved in 100 mL 1 N acetic acid, concentrated by rotary evaporation, reconcentrated repeatedly from water (13 x 100 mL) to remove ammonium acetate, and lyophilized (10 μ, 14 hours) to afford DTPA-B(AE)A • $2H_2O$. ^1H NMR (250 MHz, D_2O/DCl:pH 2.3): δ 2.95 (t, 4H, J = 5.7 Hz), δ 3.09-3.28 (b, 8H), δ 3.35 (t, 4H, J = 5.7 Hz), δ 3.51 (s, 4H), δ 3.55 (s, 2H), δ 3.66 (s, 4H).

Oligomeric polychelants comprising mono-chelating groups other than DTPA may of course be prepared using techniques analogous to those described in Examples 2 to 16 above.

Example 17

6,9,19,22-Tetrakis(carboxymethyl)-3,25-bis [2-(methylamino)-2-oxoethyl]-11,17-dioxo-14-dimethyl -3,6,9,19,22,25-hexaaza-12,16-dioxahexacosanedioic Acid (2,2-DimethylpropylDTPA-(3,25)BMA Dimer)

To a stirred solution of DTPA-MMA • H_2O (1.0 g, 2.35 mmol) in 30 mL of anhydrous pyridine at 0°C is added DCC (1.069 g, 5.15 mmol). The ice bath is removed and the mixture allowed to stir for 4 hours at ambient temperature after which time 2,2-dimethyl-1,3-propanediol (0.122g, 1.17 mmol) is added. After stirring for 24 hours at ambient temperature, the mixture is stripped to dryness, 10 mL of H_2O is added, and the white DCU precipitate is removed by filtration. Purification on ion-exchange resin followed by lyophilization provides the title dimer.

Example 18

Dy_2(PropylDTPA-(3,25)BMA) Dimer

Method 1:

PropylDTPA-(3,25)BMA dimer (636.5 mg, 0.75 mmol) and dysprosium chloride hexahydrate (564.5 mg, 1.50 mmol) are mixed in water at ambient temperature until dissolved. The solution is then adjusted to pH 7 with dilute NaOH.

Method 2:

PropylDTPA-(3,25)BMA dimer (3.8 g, 4.29 mmol) and dysprosium oxide (1.6 g, 4.29 mmol) were mixed in 14.3 mL of water and heated to 80°C for 40 hours. The solution was adjusted to pH 6.7 with dilute NaOH.

Example 19

Dy_2(PropylDTPA-(9,19)BMA) Dimer

PropylDTPA-(9,19)BMA • H_20 dimer (200 mg, 0.226 mmol) and dysprosium oxide (84.3 mg, 0.226 mmol) were mixed and stirred in 2.3 mL of water and heated to 60°C for 35 h. The pH was adjusted to 7 with dilute NaOH.

Example 20

$Hf(IV)_2$(DTPA-Octaacid) Dimer

DTPA-Octaacid dimer (1.21 g, 1.5 mmol) in 5 mL of water is treated with 1 N sodium hydroxide solution (12.0 mL, 12.0 mmol) followed by 0.5 M hafnium tetrachloride solution (6.0 mL, 3.0 mmol). The solution is stirred for 30 minutes and adjusted to pH 7 with dilute NaOH.

Although particular examples have been set forth above illustrating various embodiments of the invention, other embodiments will be recognized by the skilled practitioner and may be achieved using techniques known in the art in view of the present disclosure.

Example 21

1,4,7,10-Tetraazacyclododecane-4,7,10-triacetic acid tri-t-butyl ester

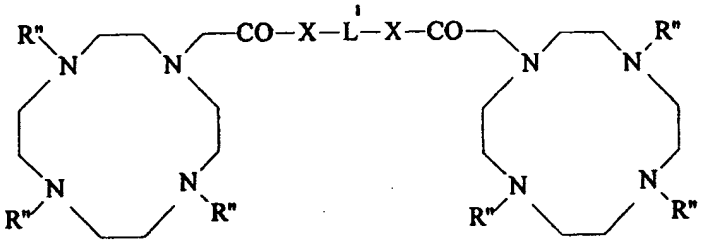
Sodium acetate (25.298 g: 0.3084 mol) was added to a stirred suspension of 1,4,7,10-tetraazacyclododecane (17.71 g; 0.1028 mol) in N,N'-dimethylacetamide (DMA) (312 mL) at ambient temperature. A solution of bromoacetic acid t-butyl ester (49.8 mL; 0.3084 mol) in DMA (160 mL) was added dropwise to the stirred mixture, and the mixture stirred at ambient temperature for 11 days. A solid precipitate was isolated by suction filtration and washed once with cold DMA (20 mL). Residual DMA was removed by heating the solid at 45°C under reduced pressure for 20 hrs. The white solid (40.18 g) was dissolved in chloroform (200 mL) and washed with deionized water (3 x 300 mL). The organic layer was dried over $MgSO_4$ and subsequently concentrated to a solid which was further dried under reduced pressure to yield the title compound as a white powder, 36.3 g (69%).

^{1}H NMR ($CDCl_3$): δ 1.42 (s, 27H); δ 2.85-2.88 (m, 12H); δ 3.06 (m, 4H); 3.25 (s, 2H); δ 3.34 (s,4H).

FAB mass spectrum, m/z: 515 (MH+).

Claims

1. A compound of formula I



(I)

(wherein XL'X is a linker moiety in which each X is oxygen or a secondary, tertiary or ring nitrogen and the molecular weight of XL'X is less than 1000; R" is a group $-CH_2COR$ in which R is OR' or NR'_2 where each R' independently is hydrogen or an alkyl, cycloalkyl, alkenyl, alkynyl or aryl group optionally substituted by hydroxyl, amine or carboxyl groups, or a carbohydrate group, a peptide or polypeptide residue, a protein or a biomolecule) or a salt or chelate thereof.

2. A compound of formula I as claimed in claim 1 wherein X is nitrogen, or a salt or chelate thereof.

3. A compound of formula I as claimed in claim 2 wherein the amide nitrogen X is a secondary nitrogen, a ring nitrogen or is a tertiary nitrogen carrying a pendant X'"R' group wherein X'" denotes a bond, an oxygen or sulphur atom or a group NR' and R' denotes a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkynyl or aryl group optionally substituted by hydroxyl, amine or carboxyl groups, or a salt or chelate thereof.

4. A compound as claimed in any one of claims 1 to 3 wherein the molecular weight of XL'X is less than 500, or a salt or chelate thereof.

5. A compound as claimed in any one of claims 1 to 4 wherein the molecular weight of XL'X is less than 150, or a salt or chelate thereof.

6. A compound as claimed in any one of claims 1 to 5 wherein XL'X provides a chain of up to 10 atoms in length between the carbonyl carbons to which the X groups are attached, or a salt or chelate thereof.

7. A compound as claimed in any preceding claim wherein R" represents a group CH_2CO_2H, or a salt or chelate thereof.

8. A compound as claimed in claim 7 being 1,8-bis[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-2,7-dioxo-3,6-diazaoctane, or a salt or chelate thereof.

9. A compound according to claim 1 comprising at least one complexed metal ion.

10. A compound according to claim 9 wherein said metal ion is selected from the group consisting of: heavy metal ions; paramagnetic metal ions; and radioactive metal ions.

11. A compound according to claim 10 comprising two said metal ions.

12. A compound according to claim 11 wherein said metal ions are lanthanide metal ions.

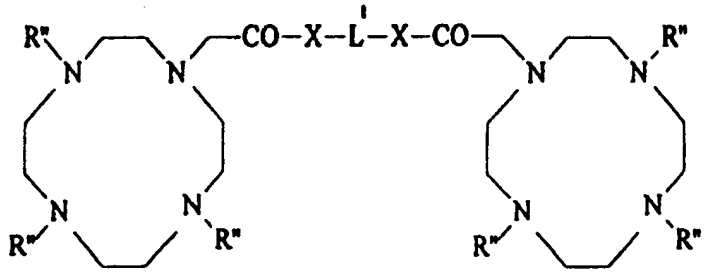
13. A compound according to claim 12 wherein said metal ions are gadolinium or dysprosium ions.

14. A magnetic resonance imaging contrast agent composition comprising a compound as claimed in claim 9, together with at least one pharmaceutical carrier or excipient.

15. Use of a compound as claimed in claim 1 or a salt or chelate thereof for the manufacture of a therapeutic or diagnostic agent for use in a method of diagnostic imaging, in radiotherapy or in heavy metal detoxification.

Patentansprüche

1. Verbindung der Formel I



worin

XL'X eine Linkereinheit ist, wobei jede Gruppe X für Sauerstoff oder einen sekundären, tertiären oder einen Ring-Stickstoff steht und wobei das Molekulargewicht von XL'X weniger als 1000 beträgt;
R" eine Gruppe $-CH_2COR$ ist, worin R für OR' oder NR'_2 steht, wobei jede Gruppe R' unabhängig voneinander für Wasserstoff oder eine gegebenenfalls durch Hydroxyl-, Amin- oder Carboxylgruppen substituierte Alkyl-, Cycloalkyl-, Alkenyl-, Alkinyl- oder Arylgruppe oder eine Kohlehydratgruppe, einen Peptid- oder Polypeptidrest, ein Protein oder ein Biomolekül steht;
oder ein Salz oder Chelat davon.

2. Verbindung der Formel I nach Anspruch 1, worin X für Stickstoff steht; oder ein Salz oder Chelat davon.

3. Verbindung der Formel I nach Anspruch 2, worin der Amidstickstoff X ein sekundärer, ein Ring- oder ein tertiärer Stickstoff mit einer Seitengruppe X'"R' ist, worin X'" eine Bindung, ein Sauerstoff- oder Schwefelatom oder eine Gruppe NR' bedeutet und R' für ein Wasserstoffatom oder eine gegebenenfalls durch Hydroxyl-, Amin- oder Carboxylgruppen substituierte Alkyl-, Cycloalkyl-, Alkenyl-, Alkinyl- oder Arylgruppe steht; oder ein Salz oder Chelat davon.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei das Molekulargewicht von XL'X weniger als 500 beträgt; oder ein Salz oder Chelat davon.

5. Verbindung nach einem der Ansprüche 1 bis 4, wobei das Molekulargewicht von XL'X weniger als 150 beträgt; oder ein Salz oder Chelat davon.

6. Verbindung nach einem der Ansprüche 1 bis 5, wobei XL'X eine Kette mit einer Länge von bis zu 10 Atomen zwischen den Carbonylkohlenstoffen, an welche die Gruppen X gebunden sind, aufweist, oder ein Salz oder Chelat davon.

7. Verbindung nach einem der vorhergehenden Ansprüche, wobei R" für eine Gruppe CH_2CO_2H steht, oder ein Salz oder Chelat davon.

8. Verbindung nach Anspruch 7, nämlich 1,8-Bis[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]-2,7-dioxo-3,6-diazaoctan; oder ein Salz oder Chelat davon.

9. Verbindung nach Anspruch 1, die wenigstens ein komplexiertes Metallion umfasst.

10. Verbindung nach Anspruch 9, wobei das Metallion ausgewählt ist unter Schwermetallionen, paramagnetischen Metallionen und radioaktiven Metallionen.

11. Verbindung nach Anspruch 10, die zwei solcher Metallionen umfasst.

12. Verbindung nach Anspruch 11, wobei die Metallionen Lanthanid-Metallionen sind.

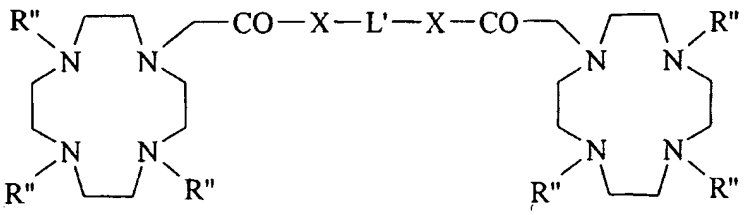
13. Verbindung nach Anspruch 12, wobei die Metallionen Gadolinium- oder Dysprosiumionen sind.

14. Magnetresnanzbildgebungs-Kontrastmittelzusammensetzung, die eine Verbindung nach Anspruch 9 zusammen mit wenigstens einer pharmazeutischen Trägersubstanz oder einem Exzipienten umfasst.

15. Verwendung einer Verbindung nach Anspruch 1 oder eines Salzes oder Chelates davon zur Herstellung eines therapeutischen oder diagnostischen Mittels zur Verwendung in diagnostischen Bildgebungsverfahren, bei der Strahlentherapie oder bei der Schwermetallentgiftung.

Revendications

1. Composé de formule I



(I)

(dans laquelle XL'X est un reste de liaison, dans lequel chaque X est un oxygène ou un azote secondaire, tertiaire ou cyclique et la masse moléculaire de XL'X est inférieure à 1000; R" est un groupe $-CH_2COR$ dans lequel R est OR' ou NR'_2, où chaque R' est indépendamment hydrogène ou un groupe alkyle, cycloalkyle, alcényle, alcynyle ou aryle éventuellement substitué par des groupes hydroxy, amine ou carboxyle, ou un groupe hydrate de carbone un résidu peptide ou polypeptide, une protéine ou une biomolécule) ou un de ses sels ou chélates.

2. Composé de formule I tel que revendiqué dans la revendication 1, dans lequel X est un azote, ou un de ses sels ou chélates.

3. Composé de formule I tel que revendiqué dans la revendication 2, dans lequel l'azote X de l'amide est un azote secondaire, un azote cyclique ou un azote tertiaire portant un groupe latéral X'"R', dans lequel X'" représente une liaison, un atome d'oxygène ou de soufre ou un groupe NR' et R' représente un atome d'hydrogène ou un groupe

alkyle, cycloalkyle, alcényle, alcynyle ou aryle éventuellement substitué par des groupes hydroxy, amino ou carboxyle, ou un de ses sels ou chélates.

4. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 3, dans lequel la masse moléculaire de XL'X est inférieure à 500, ou un de ses sels ou chélates.

5. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 4, dans lequel la masse moléculaire de XL'X est inférieure à 150, ou un de ses sels ou chélates.

6. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 5, dans lequel XL'X représente une chaîne ayant une longueur de jusqu'à 10 atomes entre les atomes de carbone carbonyle auxquels les groupes X sont liés, ou un de ses sels ou chélates.

7. Composé tel que revendiqué dans l'une quelconque des revendications précédentes, dans lequel R" représente un groupe CH_2CO_2H, ou un de ses sels ou chélates.

8. Composé tel que revendiqué dans la revendication 7, qui est le 1,8-bis[4,7,10-tris(carboxyméthyl)-1,4,7,10-tétraazacyclododéc-1-yl]-2,7-dioxo-3,6-diazaoctane, ou un de ses sels ou chélates.

9. Composé selon la revendication 1, comprenant au moins un ion métallique complexé.

10. Composé selon la revendication 9, dans lequel ledit ion métallique est choisi dans le groupe constitué par: les ions de métaux lourds; les ions de métaux paramagnétiques et les ions de métaux radioactifs.

11. Composé selon la revendication 10 comprenant deux desdits ions métalliques.

12. Composé selon la revendication 11, dans lequel lesdits ions métalliques sont des ions de métaux lanthanides.

13. Composé selon la revendication 12, dans lequel lesdits ions métalliques sont des ions de gadoliniuin ou de dysprosium.

14. Une composition d'un agent de contraste pour imagerie par résonance magnétique comprenant un composé tel que revendiqué dans la revendication 9 avec au moins un support ou excipient pharmaceutique.

15. Utilisation d'un composé tel que revendiqué dans la revendication 1 ou d'un de ses sels ou chélates pour la fabrication d'un agent therapeutique ou diagnostique pour une utilisation dans une méthode d'imagerie diagnostique, en radiothérapie ou en détoxification des métaux lourds.